Mechanism of Benzyl Migration from Nitrogen to Carbon in Enamines

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Mechanism of Benzyl Migration from Nitrogen to Carbon in Enamines

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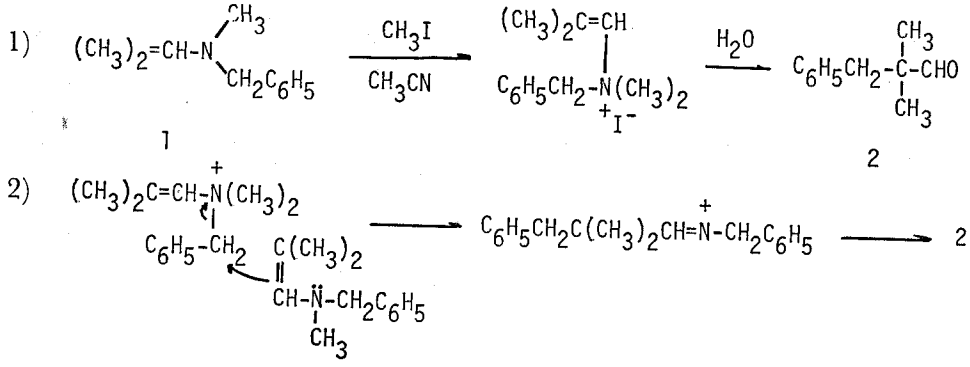
The rearrangement of (*R*)-*N*-isobutenyl-*N*-methyl-benzylamine-α-*d* was thermally effected to give (*R*)-2, 2-dimethyl-3-phenyl-propanal-*3-d* with over-all retention of configuration of the migrating terminus in 91% asymmetric yield. The stereochemical outcome in the present benzyl migration unequivocally established the mechanism to be the sequential *N*-alkylation, retrogressive dissociation and *C*-alkylation, with two Walden inversions involved in the process.

INTRODUCTION

In connection with our study[1] on the reaction of chiral enamines, it seemed of interest to undertake the elucidation of mechanism of the thermally induced benzyl migration from nitrogen to carbon in enamines.

An example of such rearrangements was demonstrated by Brannock[2] who treated *N*-isobutenyl-*N*-methyl-benzylamine (**1**) with methyl iodide in acetonitrile to afford *N*-isobutenyl-*N*-methyl-3-phenyl-propanal (**2**) after hydrolysis of the rearrangement product.

However, three different mechanisms have been proposed for the rearrangements of this category: 1) a direct intramolecular 1,3-shift of benzyl group from nitrogen to carbon (mechanism 1)[3]; 2) a partial retrogressive dissociation of the first formed ammonium salt into enamine and benzyl halide, followed by an intermolecular nucleophilic displacement between enamine and the ammonium salt (mechanism 2)[4]; 3) a prior *N*-alkylation of enamine and subsequent retrogressive dissociation, followed by *C*-alkylation of enamine with benzyl halide (mechanism 3).[4] Although these proposals are all seemingly successful in explaining the rearrangement leading to the end product, no convincing evidence has been presented for each mechanism.



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3) $(CH_3)_2CH{=}CH{-}\overset{+}{N}(CH_3)_2$ $I^-\rightarrow CH_2C_6H_5$ $\rightleftharpoons$ $(CH_3)_2C{=}CH{-}N(CH_3)_2$ + $C_6H_5CH_2I$ $\longrightarrow$ $C_6H_5CH_2C(CH_3)_2CH{=}\overset{+}{N}(CH_3)_2I^-$ $\longrightarrow$ 2

Should the intramolecular 1,3-shift mechanism 1 be valid for the present rearrangement, inversion of configuration at the migrating terminus would be duly expected from the Woodward-Hoffmann rule.[5] The inversion would be predicted also for the intermolecular nucleophilic displacement (mechanism 2). In contrast, if the reaction should proceed through the last pathway (mechanism 3), the over-all retention of configuration at the migrating terminus would result from two consecutive Walden inversions involved in the process.

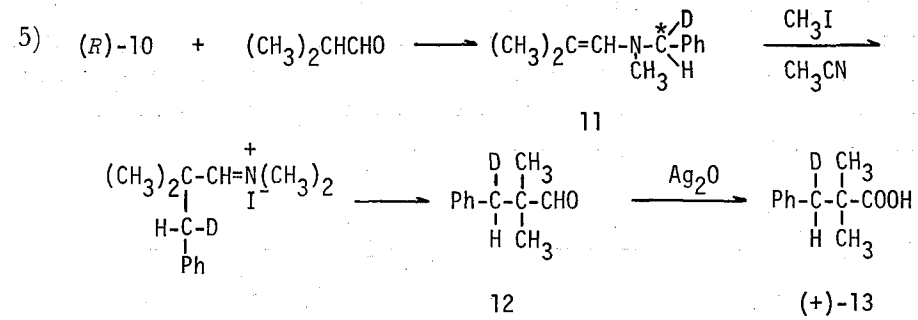
In view of *a priori* consideration mentioned above, we preferred the stereochemical means with an optically active enamine whose chirality was due to the replacement of one hydrogen by deuterium.

RESULTS AND DISCUSSION

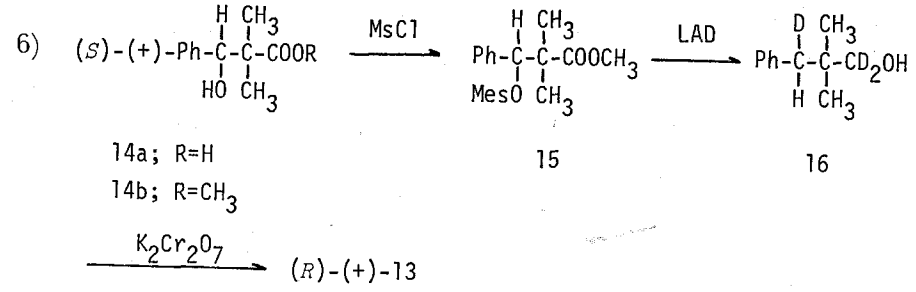
The chiral enamine subjected to thermal rearrangrment was (*R*)-*N*-isobutenyl-*N*-methyl-benzylamine-α-*d* (**11**), prepared from (*R*)-(−)-*N*-methylbenzylamine-α-*d* (**10**) and isobutyraldehyde according to scheme 4. For the preparation of isotopically pure benzylamine-α-*d* (**9**), an enzymic process was incorporated with synthesis; 2-phenyl-2-morpholinoacetonitrile (**3**) was deuterated with deuterium oxide at 100°C in DMF to give the nitrile **4**, which on hydrolysis, afforded nearly completely deuterated benzaldehyde (**5**).[6] Enantiomerically pure (*S*)-(+)-benzyl-α-*d* alcohol (**6**), $[\alpha]_D$ 1.45°, was obtained by reduction of **5** with fermenting bakers' yeast.[7] The benzyl alcohol (*S*)-(+)-**6** was converted to the azide **8** via the thermolabile tosylate **7**. The lithium aluminum hydride reduction of the azide gave (*R*)-(−)-amine **9**, $[\alpha]_D$ −1.7°, which on *N*-methylation, afforded the desired *N*-methyl-benzylamine-α-*d* (**10**), $[\alpha]_D$ −2.88°. Since it has been established[8] that the reaction of azide ion proceeds with inversion of configuration, the levorotatory amine (**10**) can be assigned the *R*-configuration. The chiral enamine **11** was finally obtained by the condensation of isobutyraldehyde with (*R*)-(−)-**10**.

4) Ph-C(H)(CN)-N⟨O⟩ (**3**) $\xrightarrow[DMF]{D_2O}$ Ph-C(D)(CN)-N⟨O⟩ (**4**) $\xrightarrow{H^+}$ Ph-CDO (**5**) $\xrightarrow{yeast}$ D-C(H)(Ph)-OH (+)-*S*-**6** $\xrightarrow{TsCl}$ D-C(H)(Ph)-OTs (**7**) $\xrightarrow{NaN_3}$ Ph-C(H)(D)-N_3 (**8**) $\xrightarrow{LAH}$ Ph-C(H)(D)-NH_2 (−)-*R*-**9** $\xrightarrow[2)LAH]{1)HCOOH}$ Ph-C(H)(D)-$NHCH_3$ (−)-*R*-**10**

The rearrangement of the chiral enamine **11** was thermally effected under the literature conditions[2] to give (+)-2, 2-dimethyl-3-phenyl-propanal-*3-d* (**12**). Oxidation of **12** with silver oxide gave (+)-2, 2-dimethyl-3-phenylpropionic-*3-d* acid (**13**) in 43% yield, $[\alpha]_D$ 1.65°.



The absolute configuration of (+)-**13** was determined by the correlation to (*S*)-(+)-2, 2-dimethyl-3-hydroxy-3-phenylpropionic acid (**14a**) of the well-defined *S*-configuration.[9] According to scheme 6, (*S*)-(+)-**14a**, $[\alpha]_D$ 8.3°, was obtained by the Reformatsky reaction[10] of 2-bromo-isobutyric acid with benzaldehyde, followed by optical resolution with (−)-methylbenzylamine. The (+)-acid was transformed to the mesylate **15**, which was then reduced with lithium aluminum deuteride to the dextro-rotatory alcohol **16**, $[\alpha]_D$ 6.1°. Finally, the oxidation of (+)-**16** with potassium bichromate afforded the (+)-acid **13**, $[\alpha]_D$ 1.78° which proved to be identical with that **13** derived from the rearrangement product.



On the basis of this chemical conversion, the acid (+)-**13** can be assigned the *R*-configuration, since the *S*-configuration of (+)-**14a** has been unequivocally established and a Walden inversion at the LAD reduction step[11] was involved in the transformation. The enantiomeric purity is assessed to be 91% based on the maximum rotation 9.02° of the starting acid **14a**.

Accordingly, the chiral enamine (*R*)-**11** rearranged on heating to the *R*-product, which means that the present thermal rearrangement proceeds with retention of configuration at the migrating terminus Ph-$\overset{*}{C}$HD, the Cahn-Ingold-Prelog sequence of ligands at the chiral centers being the same before and after the rearrangement.

The present stereochemical outcome thus argues against both intra-and intermolecular migrations of benzyl group which should have been accompanied by inversion of configuration (mechanisms 1 and 2), and cogently supports the last mechanism

involving the prior *N*-alkylation, retrogressive dissociation, followed by *C*-alkylation.

Further support for this deduction was furnished by the following studies. The corresponding perchlorate **18**, derived from the iodide salt **17** by exchange with silver perchlorate, was found completely inert to heating, no alkylated aldehyde having been detected in the hydrolyzate of the reaction mixture (scheme 7). Since no one can find apparent reason why the intramolecular N→C shift should be prohibited upon exchanging the gegen anion from iodide to perchlorate, the result, though negative, excludes a direct benzyl group migration defined as 1, 3-sigmatropic rearrangement which demands a suprafacial allylic shift.

7) $(CH_3)_2C{=}CH\text{-}\overset{+}{N}(CH_3)\text{-}CH_2Ph\ I^-$ (17) $\xrightarrow{AgClO_4}$ $(CH_3)_2C{=}CH\text{-}\overset{+}{N}(CH_3)\text{-}CH_2Ph\ ClO_4^-$ (18) ⟶ 2

To obtain more information concerning the mechanism, a crossover-recombination experiment was designed: a) an intimate mixtre of 1-*N*-morpholino-isobutene-1 (**19**) and 1-morpholino-2-ethyl-butene-1 (**20**) was allowed to react with an equimolar benzyl bromide and *p*-methylbenzyl bromide. b) A mixture of the salts **21** and **22** which were readily prepared from the enamines **19** and **20** with the corresponding bromides, was heated in exactly the same manner. In both reactions, the hydrolysis of reaction mixtures resulted in the formation of four cross-hybrids, 2, 2-dimethyl-3-phenyl-propanal (**2**), 2, 2-dimethyl-3-*p*-xylyl-propanal (**23**), 2-ethyl-2-benzyl-butyraldehyde (**24**) and 2-ethyl-2-*p*-xylyl-butyraldehyde (**25**) in nearly the same distribution as proved by vpc-analysis. (Table I). The same product distribution found for these two reactions clearly shows the congruency of operating species in both systems, which again excludes the direct intramolecular migration of benzyl group and favors the retrogressive dissociation mechanism.

Table I. Product Distribution in Cross-Over Recombination

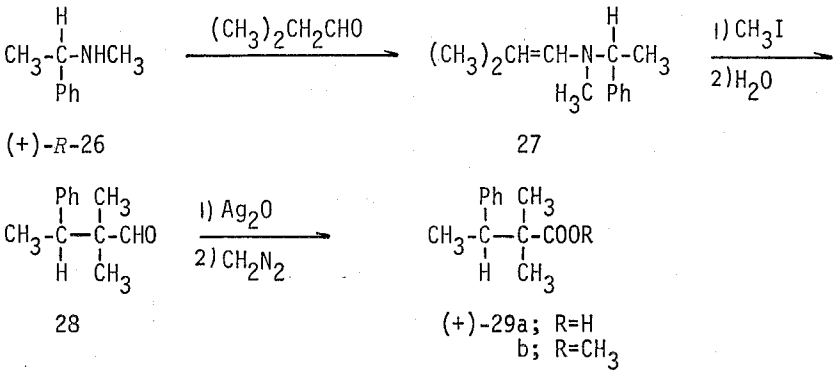
System	Products			
	2	**23**	**24**	**25**
I	3.0	3.1	1.0	1.1
II	2.6	2.7	1.0	1.2

$(CH_3)_2C{=}CH$-molph. (19), $(C_2H_5)_2C{=}CH$-molph. (20) were used in system I and $(C_3H)_2C{=}CH\text{-}\overset{+}{N}(CH_2Ph)\bigcirc O$ (21), $(C_2H_5)_2C{=}CH\text{-}\overset{+}{N}(CH_2Ph\text{-}p\text{-}CH_3)\bigcirc O$ (22) in system II. 2; $PhCH_2C(CH_3)_2CHO$, 23; $p\text{-}CH_3\text{-}PhCH_2C(CH_3)_2CHO$, 24; $PhCH_2C(C_2H_5)_2CHO$, 25; $p\text{-}CH_3\text{-}PhCH_2C(C_2H_5)_2CHO$.

Additional evidence for the mechanism was provided also by another asymmetric system, with *N*-methyl-methylbenzylamine (**26**) used as the chiral migrating group. When the chiral enamine **27**, prepared from (*R*)-(+)-*N*-methyl-methylben-

zylamine (**26**), $[\alpha]_D$ 54.4° and isobutyraldehyde, was heated with methyl iodide, the aldehyde **28** was obtained after the usual work-up of the reaction mixture. This was transformed by silver oxide oxidation to the acid **29a**, whose esterification with diazomethane afforded methyl 2, 2-dimethyl-3-phenylbutyrate (**29b**), $[\alpha]_D$ 15.67°.

8)

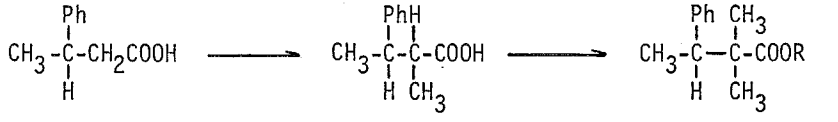


(+)-*R*-26 27

28 (+)-29a; R=H, b; R=CH_3

The absolute configuration of the acid **29a** was correlated to the known (+)-phenylbutyric acid[12] (**30**) according to scheme 9: (*S*)-(+) acid **30** $[\alpha]_D$ 52.4° was converted into (+)-**29** $[\alpha]_D$ 33.48°, via α-mono methylated acid **31**, by means of exhaustive α-methylation with methyl iodide, sodium hydride and butyllithium. The configuration of the chiral center in (*S*)-(+)-**30** is not disturbed during this process and is retained as such in the alkylated product **29**, but the sequence of ligands at the chiral center in **30** is reversed in the product **29**. So that the *R*-configuration is assigned to (+)-**29** and the enantiomeric purity is assessed to be 45% based on that of the starting acid **30**.

9)



(+)-*S*-30 31 (+)-*R*-29a and b

Consequently, here again the rearrangement of **26** to **28** proceeded with retention of configuration, in conformity with the deduced mechanism. The observed lowering in asymmetric yield may probably be due to the extreme ease with which the intermediately formed α-methylbenzyl iodide undergoes racemization.

In conclusion, all the experimental evidence presented in the present study supports the mechanism involving a prior *N*-quarternization with methyl iodide, and subsequent nucleophilic attack of iodide to the chiral benzylic carbon with liberation of benzyl iodide which in turn undergoes a nucleophilic displacement by enamine. This is consistent with the mechanism proposed by Pandit[13] for alkylation of dienamines.

EXPERIMENTAL

The melting and boiling points were uncorrected. Ir-spectra were recorded with a Hitachi 215 spectrophotometer. Pmr-spectra were taken on a Varian EM-360 spectrometer. Elemental analyses were carried out with a Yanagimoto CHN-corder TM-1. Optical rotations were observed on a Yanagimoto OR-50 and a Perkin Elmer R-241. Gas liquid chromatography was on a Shimazu Model 4BPF and a Varian Aerograph A-700.

(*R*)-(−)-*N*-Methyl-benzylamine-*α*-*d* (**10**). The titled compound was prepared by the following processes. (a) (*S*)-(+)-Benzyl-*α*-*d* alcohol (**6**), $[\alpha]_D^{24}$ +1.43°, (neat), was obtained by the prescribed procedure[7] from benzaldehyde-*α*-*d* (**5**). (b) Benzyl-*α*-*d* tosylate (**7**). The alcohol **6** (2.1 g) was added to *p*-toluenesulfonyl chloride (2.9 g) in 25% aqueous sodium hydroxide with stirring at 5°C. After 1.5 hr, an equivalent amount of the chloride in 25% aq. sodium hydroxide was added to the reaction mixture, which was then stirred for further 3 hr at 5°C. The product was poured into ice-water and was extracted with ether. Removal of solvent gave the crystalline tosylate **7**. (c) Benzyl-*α*-*d* azide (**8**). The crude tosylate **7** was added to a solution of sodium azide (2 g) in water (5.8 ml) and methanol (26 ml). After stirring at 60°C for 24 hr, the reaction mixture was treated with ice-water and was extracted with ether. Removal of solvent gave an oily product, which was unstable at room temperature, so that it was subjected to the following reduction without further purification. (d) (*R*)-(−)-Benzylamine-*α*-*d* (**9**). The reduction of the azide **8** with LAH gave the corresponding amine as an oil in 40% yield: bp 79–81°C (20 Torr), n_D^{25} 1.5412, $[\alpha]_D^{25}$ −1.79° (neat). The ir-spectrum was identical with that of the authentic sample.[14] (e) (*R*)-(−)-*N*-Methyl-benzylamine-*α*-*d* (**10**). The methylation of the amine **9** (1 g) by treating with formic acid (0.5 ml) and formaldehyde (1.2 ml), followed by the LAD reduction, afforded the titled amine **10** in 90% yield. $[\alpha]_D^{25}$ −2.88° (neat), pmr (in $CDCl_3$): δ, 3.52 (s, 3H, N-CH_3).

N-Isobutenyl-*N*-methyl-benzylamine-*α*-*d* (**11**). (*R*)-(−)-*N*-Methyl-benzylamine-*α*-*d* (**10**, 1.2 g) was allowed to react with an equimolar isobutyraldehyde (0.6 g) in benzene according to the procedure of Benzing.[15] The product was purified by distillation under reduced pressure; bp 54–56°C (1 Torr) yield 2 g (90%), ir: no absorption band at 1700 cm^{-1} due to $\nu_{C=O}$, $\nu_{=O}$ at 1620 cm^{-1}.

(+)-2, 2-Dimethyl-3-phenylpropionic-*3*-*d* acid (**13**). The thermal rearrangement of the enamine **11** (2 g) was effected by the literature procedure to give 2, 2-dimethyl-3-phenylpropanal-*3*-*d* (**12**) in 43% yield: The silver oxide oxidation of the aldehyde **12** afforded the acid **13**, whose specific rotation did not alter on repeated recrystallizations from benzene. Yield 300 mg: mp 46–48°C: $[\alpha]_D^{28}$ +1.65° (*c*, 1.0, MeOH), ir: ν_{OH} 3000 and 1710 cm^{-1}. pmr ($CDCl_3$): δ, 1.26 (s, 6H, $2CH_3$), 2.56 (broad s, IH, CH), 7.27 (s, 5H, aromatic protons) and 10.33 (s, IH, COOH). Found: C, 73.74; H, 8.16. Calcd for $C_{11}H_{13}O_2D$: C, 73.71; H, 7.94%.

Absolute assignment of configuration to (+)-2, 2-dimethyl-3-phenylpropionic-*3-d* acid (**13**). (*S*)-(+)-3-Hydroxy-2, 2-dimethyl-3-phenylpropionic acid[9] (**14a**, $[\alpha]_D^{23}$ +8.3° (*c*, 2.88, AcOH) prepared by resolution of the racemate[10] with (*S*)-(−)-methylbenzylamine, was esterified with diazomethane to the methyl ester **14b**, $[\alpha]_D^{23}$ +27.2° (*c*, 2.2, chloroform). The methyl ester (1 g) was allowed to react with mesyl chloride (2.4 g) in pyridine (25 ml) at −5°C for 3 days to give the mesylate **15**. The completion of reaction was checked by the disappearance of OH signal in pmr spectrum. Subsequent reduction of the mesylate with LAD (700 mg) afforded the corresponding alcohol **16**, $[\alpha]_D$ +6.10°, which was further oxidized with potassium bichromate to the acid (+)-**13**, yield 210 mg, mp 46–48°C, $[\alpha]_D$ +1.78°. The ir and pmr spectra were superimposable with those obtained from the rearrangement. Found: C, 73.73; H, 8.23. Calcd for $C_{11}H_{13}O_2D$: C, 73.71: H, 7.94%.

(*R*)-(+)-*N*-Isobutenyl-methyl-methylbenzylamine (**27**). This enamine was obtained by the reaction of *N*-methyl-methylbenzylamine (**26**, 10 g) with isobutyraldehyde (20 g) in benzene according to the Benzing's procedure;[15] bp 125–8°C (25 Torr), n_D^{25} 1.4852, yield 13.8 g, ir: $\nu_{C=C}$ 1635 cm^{-1}.

(*R*)-(+)-2, 2-Dimethyl-3-phenylbutyric acid (**29a**) and its methyl ester (**29b**). Methyl iodide (19 g) was added to the chiral enamine (**27**, 20 g) in acetonitrile (50 ml) with cooling. The mixture was heated under reflux for 20–24 hr. The usual work up gave the crude aldehyde **28**, bp 104–105°C (10 Torr), yield 6.51 g (34%), $[\alpha]_D^{23}$ +20.58° (*c*, 1.0, MeOH). The crude aldehyde **28** was oxidized with silver oxide to give the corresponding acid **29a**, which was esterified with diazomethane. The analytical sample of methyl ester was obtained by preparative vpc (5% PEG, column length 2m, oven-temperature 180°C, He 1.2 kg/cm^2); $[\alpha]_D^{25}$ 15.67° (*c*, 1.0, MeOH), pmr ($CDCl_3$): δ, 1.05 (d, 3H, $CHC\underline{H}_3$), 1.20 (d, 6H, $C(CH_3)_2$), 3.05 (m, 1H, CH), 3.51 (s, 3H, $COOCH_3$) and 7.25 (s, 5H, aromatic protons).

Conversion of (*S*)-(+)-phenylbutyric acid (**30**) to (+)-2, 2-dimethyl-3-phenylbutyric acid (**29**). (a) 2-Methyl-3-phenylbutyric acid (**31**). (*S*)-(+)-Phenylbutyric acid[12] (**30**, 8.2 g), $[\alpha]_D$ 52.4°, was added to the solution of sodium hydride (12 g) and diisopropylamine (5.05 g) in absolute THF (50 ml). After heating for 5 min., *n*-butyl lithium (16 g) was added with cooling below 10°C. After warming the reaction mixture for 5 min., methyl iodide (7.1 g) was added with external cooling and the whole was stirred for additional 3 hr at 30°C. By a usual work-up, the methylated acid **31** was recovered (9 g). Colorless needles, mp 126–8°C. Found: C, 74.37; H, 8.14%. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92%. b) 2, 2-Dimethyl-3-phenylbutyric acid (**29a**). The treatment of the mono-methylated acid **31** in the same manner as described above afforded 2, 2-dimethylated acid **29a**, bp 154–156°C (6 Torr). The pmr spectrum was consistent with that of the rearrangement product. Found: C, 74.64; H, 8.20%. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%. The pmr spectrum of the methylester **29b**, $[\alpha]_D^{16}$ 33.48° (*c*, 2.03, MeOH), was identical with that of the sample derived from the rearrangement product.

Crossover-recombination experiment. Materials: 1-*N*-Morpholino-2-methyl-1-propene (**19**), bp 97–98°C (30 Torr), n_D^{20} 1.4193 and 1-*N*-morpholino-2-ethyl-1-butene (**20**), bp 103–105°C (40 Torr), n_D^{20} 1.4310 were prepared according to the literature.[15] Ir spectra of these enamines were identical with those reported in the literature.[16] The salts **21** and **22** were prepared from enamines and the corresponding bromides, i.e. benzyl bromide and *p*-methylbenzyl bromide in chilled ether solution. The structures were fully substantiated by their pmr spectra. Salt **21**; mp 185°C (decomp.), pmr ($CDCl_3$): δ, 1.25 (d, 6H, $C(CH_3)_2$), 4.61 (s, 2H, CH_2), 7.50 (s, 5H, aromatic protons). Salt **22**; mp 190°C (decomp.), pmr ($CDCl_3$); δ, 1.15 (m, 6H, $C(CH_3)_2$), 2.40 (s, 3H, Ph-CH_3), 2.60 and 3.75 (m, 4H, $(CH_2)_2$), 4.46 (s, 2H, Ph-CH_2) and 7.30 (m, 5H, aromatic protons).

Products. Aldehydes **2**, **23**, **24** and **25** were obtained in the crossover-recombination experiments. The ir spectra and the retention times of the glc peaks (5% PEGS, 2 m, 180°C, He 1.0 atm/cm^2) of these cross hybrids were coincident with those of the authentic samples. 3-Phenyl-2, 2-dimethylpropanal (**2**): bp 103–105°C (10 Torr.), retention time, 7 min., 2, 4-dinitrophenylhydrazone, mp 154–155°C, Found: C, 59.71; H, 5.36; N, 16.18%. Calcd for $C_{17}H_{18}N_4O_4$: C, 56.64; H, 5.30; N, 16.37%.

3-*p*-Xylyl-2, 2-dimethylpropanal (**23**), bp 115–117°C (10 Torr), retention time, 9.4 min., 2, 4-dinitrophenylhydrazone; mp 158–160°C. Found: C, 60.45; H, 5.31; N, 15.61%. Calcd for $C_{18}H_{20}N_4O_4$: C, 60.67; H, 5.62; N, 15.17%. 2-Benzyl-2-ethylbutyraldehyde (**24**): bp 124–126°C (10 Torr), retention time, 12 min.,2, 4-dinitrophenylhydrazone, mp 122–123°C. Found: C, 61.37; H, 5.84; N, 15.07%. Calcd for $C_{19}H_{22}N_4O_4$: C, 61.61; H, 5.99; N, 15.13%.

2-*p*-Methylbenzyl-2-ethylbutyraldehyde (**25**): bp 135–137°C (10 Torr), retention time, 16.4 min, 2, 4-dinitrophenylhydrazone, mp 135–136°C. Found: C, 62.30; H, 6.15; N, 14.62%. Calcd for $C_{20}H_{24}N_4O_4$: C, 62.50; H, 6.25; N, 14.60%.

REFERENCES

(1) T. Igarashi, J. Oda, Y. Inouye, and M. Ohno, *Agr. Biol. Chem.*, **34**, 811 (1970); T. Igarashi, J. Oda, and Y. Inouye, *Bull. Inst. Chem. Res., Kyoto Univ.*, **50**, 222 (1972).

(2) K. C. Brannock and R. D. Burpitt, *J. Org. Chem.*, **26**, 3576 (1961).

(3) J. Szmuszkoviez, "Advances in Org. Chem.", vol. **4**, Interscience Pub., John Wiley & Sons. Inc., New York, 1963, p. 27.

(4) H. O. House, "Modern synthetic reactions", W. A. Benjamin, Inc., California, 1972, p. 579.

(5) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie GmbH, Academic Press Inc., 1970, p. 119.

(6) D. J. Bennet, G. W. Kirby, and V. A. Moss, *J. Chem. Soc.*, 2049 (1970).

(7) V. E. Althouse, D. M. Feigl, W. A. Sanderson, and H. S. Mosher, *J. Amer. Chem. Soc.*, **88**, 3595 (1966).

(8) P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold, and P. A. D. Rao, *Nature*, **166**, 179 (1950).

(9) M. Matell, *Ark. Kemi.*, **1**, 455 (1950).

(10) R. L. Shrinker, "Org. Reaction" New York, vol. **1**, (1942), p. 1.

(11) D. J. Prescott and J. L. Rabinowitz, *J. Biol. Chem.*, **243**, 1551 (1968).

(12) V. Prelog and H. Scherrer, *Helv. Chim. Acta*, **42**, 2227 (1959).

(13) U. K. Pandit, W. A. Zwart Voorspuij, and P. Houdewind, *Tetrahedron Lett.*, 1997 (1972).
(14) A. Streitwieser and J. R. Wolfe, *J. Amer. Chem. Soc.*, **85**, 3263 (1963).
(15) E. Benzing, *Angew. Chem.*, **71**, 521 (1959).
(16) G. Opitz, H. Hellmann, and H. W. Shubert, *Ann.*, **623**, 447 (1959).